Neuronal 5-HT Receptors and SERT

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Introduction

5-hydroxytryptamine (5-HT, serotonin) is an ancient biochemical manipulated through evolution to be utilized extensively throughout the animal and plant kingdoms. Mammals employ 5-HT as a neurotransmitter within the central and peripheral nervous systems, and also as a local hormone in numerous other tissues, including the gastrointestinal tract, the cardiovascular system and immune cells. This multiplicity of function implicates 5-HT in a vast array of physiological and pathological processes. This plethora of roles has consequently encouraged the development of many compounds of therapeutic value, including various antidepressant, antipsychotic and antiemetic drugs.

Part of the ability of 5-HT to mediate a wide range of actions arises from the imposing number of 5-HT receptors.¹ Numerous 5-HT receptor families and subtypes have evolved. Currently, 18 genes are recognized as being responsible for 14 distinct mammalian 5-HT receptor subtypes, which are divided into 7 families, all but one of which are members of the G-protein coupled receptor (GPCR) superfamily. The exception is the 5-HT₃ receptor, a Cys-loop ligand-gated ion channel (LGIC) that in evolutionary terms arose independent of the GPCR 5-HT receptors along with other members of this superfamily (e.g. the nicotinic acetylcholine receptor, GABAₐ receptor, glycine receptor and the Zn²⁺-activated receptor). Further receptor heterogeneity is generated through alternative splicing (e.g. 5-HT₃, 5-HT₄ and 5-HT₇ receptors), RNA editing (the 5-HT₂C receptor), and the putative formation of homo- and heterodimers (5-HT₂ and the β₂ adrenoceptor).²

The 5-HT₁ Receptor Family

This family consists of five separate gene products: 5-HT₁A, 5-HT₁B, 5-HT₁D, 5-HT₁E and 5-HT₁F receptors.
Previously, some of these were thought to be species-specific homologs (e.g. 5-HT$_{1A}$ receptor in rats and 5-HT$_{1D}$ receptor in humans), but the genes for each of these receptors are now known to be present in every mammalian species examined so far. Each is encoded by a single, intron-less reading frame and they share considerable sequence homology. All of these receptors couple to G$_{i/o}$ to inhibit adenyl cyclase and reduce cAMP levels, but additional signal transduction mechanisms have also been described. While their gene structure and molecular properties are similar, important cellular differences and distinct patterns of regional expression in the body underlie divergent physiological features. Several of these receptors are well known as autoreceptors that regulate the excitability of serotonin neurons and the release of serotonin, but also they are expressed in nonserotonergic neurons, where they can have analogous effects on other neurotransmitters.

**5-HT$_{1A}$ Receptors**

5-HT$_{1A}$ receptors are distributed broadly in the CNS, found in the soma, dendrites and in some cases the axon hillock of neurons, and the cell body and processes of astrocytes. This receptor is expressed by all serotonin neurons (as autoreceptors) and by many nonserotonergic neurons (as heteroreceptors). The electrophysiological effect of 5-HT$_{1A}$ receptor activation on neurons is generally inhibitory and acts by reducing neuronal firing rate. A number of highly selective ligands have been developed, and they range from full agonists to partial agonists, antagonists, and inverse agonists. 5-HT$_{1A}$ receptors are thought to be therapeutic targets for several neuropsychiatric disorders including anxiety, depression, and schizophrenia. Clinically used ligands include some of the atypical antipsychotics, which have partial agonist or neutral antagonist activity and buspirone, a partial agonist that is used for generalized anxiety disorder. 5-HT$_{1A}$ receptor partial agonists are clinically useful anxiolytic drugs and may act on the autoreceptors to reduce serotonergic activity, whereas 5-HT$_{1A}$ receptors in the hippocampus have been implicated in the mechanism of antidepressant action (by facilitating neurogenesis) and in regulating the hypothalamic-pituitary-adrenal axis. Other physiological effects of CNS 5-HT$_{1A}$ receptor activation include hypothermia, hyperphagia, and serotonin syndrome. 5-HT$_{1A}$ receptor knockout mice have heightened anxiety and may exhibit diminished depression-like features. As with the other serotonin receptors this may involve receptor actions during early brain development as well as during processing of emotional experience in the adult. A number of highly selective ligands for 5-HT$_{1A}$ receptors have been developed, although it should also be noted that some of these share affinity for 5-HT$_{7}$ receptors (e.g. 8-OH-DPAT) and others for other 5-HT$_{1}$ or 5-HT$_{2}$ receptors. WAY 100635 has often been used as a highly selective 5-HT$_{1A}$ receptor neutral antagonist. Xaliprodan and S-14506 are selective agonists.

**5-HT$_{1B}$ Receptors**

5-HT$_{1B}$ receptors are also distributed broadly in the CNS in serotonergic and nonserotonergic neurons; these receptors are predominantly translocated to axon terminals, so there is an anatomical mismatch between the localization of mRNA and mature 5-HT$_{1B}$ receptor protein. Historically the 5-HT$_{1B}$ receptor was thought to be the rat analog of 5-HT$_{1D}$ receptors, but it is now clear that both receptors are present in all mammalian species examined and their regional distributions differ. β-adrenergic antagonists have high affinity for 5-HT$_{1B}$ receptors in some but not all species. 5-HT$_{1B}$ autoreceptors have been found to reduce 5-HT synthesis and release and enhance reuptake via the serotonin transporter. 5-HT$_{1B}$ heteroreceptors inhibit the release of a range of different neurotransmitters, depending on the neuron types that express them. Systemic administration of 5-HT$_{1B}$ receptor agonists have several behavioral effects including increased locomotion, changes in brain reward mechanisms, and decreased aggression, whereas selective antagonists may have some procognitive potential. The expression of these receptors in diverse and potentially competing sets of neurons may impact their utility as a clinical target, although several 5-HT$_{1B,D}$ receptor agonists are effective as antimigraine treatments. 5-HT$_{1B}$ receptor knockout mice have been tested extensively and have a distinct phenotype characterized by increased aggression and, in most cases, predisposition for addiction-like behaviors. Their phenotype may...
however depend on compensatory changes in the dopamine system during development rather than being due to decreased 5-HT₁B receptor signaling in adults. Several moderately selective agonists have been developed, including CP 93129 and the more brain-penetrant CP 94253, and antagonists such as SB 224289 are used commonly to identify 5-HT₁B receptor-mediated responses.

5-HT₁D Receptors

5-HT₁D receptors are expressed at more modest levels than 5-HT₁B receptors in the brain, but the largest extent of expression seems to be in the raphe nuclei. Similarly, 5-HT₁D receptor binding sites are present at a lower level than 5-HT₁B receptor binding sites in most brain areas. Most evidence, using 5-HT₁B receptor knockout mice as controls, indicates that terminal serotonin autoreceptor activity in the forebrain is of the 5-HT₁B receptor type, but there may be somatodendritic 5-HT₁D autoreceptors that regulate serotonin release within the raphe nuclei. The dilemma for most putative selective 5-HT₁D receptor ligands is that they have high affinity for more than one receptor, usually either the 5-HT₁B or 5-HT₁A receptors, but often not both, allowing combinations of drugs to achieve conditions that are reasonably selective for activation or inhibition of 5-HT₁B receptors. Interestingly, ketanserin has ~100-fold higher affinity for human 5-HT₁D than 5-HT₁B receptors, but it has the highest affinity for 5-HT₂A receptors.

5-HT₁E Receptors

The lower case letters denote that this receptor has not been confirmed to have meaningful physiological functions in vivo. The existence of this receptor was originally postulated based on radioligand binding studies using brain homogenates, indicating that a 5-HT₁-like receptor with low affinity for 5-carboxamidotryptamine could be demonstrated. It is now clear that several binding sites might have contributed to this observation. The gene sequence for the 5-HT₁E receptor has been cloned from a human placental library and guinea pig brain genomic DNA but was undetectable in rat and mouse. There have been few pharmacological studies of this receptor in rodents or in human tissue, but it was detected by RT-PCR in various brain regions of guinea pig and in the human and monkey brain by in situ hybridization. Furthermore, no highly selective ligands have been developed, although a number of typical 5-HT₁ receptor agonists and antagonists display modest affinity at these receptors in heterologous expression systems. A recent method for labeling 5-HT₁E binding sites in guinea pig was recently described and may be a useful strategy for modeling human 5-HT₁E receptors. The physiological significance of this receptor therefore remains uncertain.

5-HT₁F Receptors

The 5-HT₁F receptor has been detected in multiple species and has been cloned from human, rat, guinea pig, and mouse genomes. Like other members of the 5-HT₁ receptor family, this receptor inhibits adenylyl cyclase via a G-coupled mechanism. It is expressed at modest levels in the CNS in both serotonergic and nonserotonergic cell bodies where it acts as both an autoreceptor and heteroreceptor, respectively. Like 5-HT₁B receptors, 5-HT₁F is expressed in trigeminal ganglion and vestibular nuclei neurons and has a high affinity for triptan drugs that are useful for the treatment of migraine headache. The relative contribution of each of these two receptors to pain relief in migraine has not been resolved. It is possible that less selective agonists that can potentially activate multiple 5-HT₁ receptors (e.g. 5-HT₁B/D/V subtypes, such as the ‘triptans’) may relieve migraine headaches via multiple mechanisms; therefore, more selective drugs may have distinct clinical efficacy and side effect profiles. For example, the relatively selective 5-HT₁F Receptor agonist LY 334370, which has ~100-fold higher affinity for 5-HT₁F over 5-HT₁B receptors, is active in animal models of anti-migraine activity but seems to act on the trigeminal nucleus rather than through a vascular mechanism. To date, no selective 5-HT₁E antagonists have been identified.
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structural conformations which have been resolved by X-ray crystallography in some cases. Structure-activity models have also been tested using site directed mutagenesis. A great deal of biophysical information has been generated using molecular strategies and heterologous expression of 5-HT\textsubscript{2A} receptors. Furthermore, simultaneous analysis of multiple signal transduction mechanisms in cell culture systems has shown that the same ligand may have differing degrees of intrinsic activity for the activation of different second messenger systems by the same population of 5-HT\textsubscript{2A} receptors.

The 5-HT\textsubscript{2} Receptor Family

The 5-HT\textsubscript{2} family has three members, 5-HT\textsubscript{2A}, 5-HT\textsubscript{2B} and 5-HT\textsubscript{2C} receptors. Their pharmacological significance is substantial due to both the clinical importance and complex pharmacological features of these receptors. 5-HT\textsubscript{2} receptors were originally posited based on an important study by Gaddum and Picarelli in 1957\textsuperscript{15}. Using a guinea pig ileum contraction bioassay, they observed two classes of ‘tryptamine’ receptors (namely ‘M’ and ‘D’) that correspond to 5-HT\textsubscript{3} and 5-HT\textsubscript{2} receptors in current nomenclature. Constituents of the 5-HT\textsubscript{2} receptor family share similar sequence homology, structural motifs, and overlapping pharmacology, although considerable ligand development has occurred and highly selective ligands are available.\textsuperscript{16} Some of the notable features of these receptors include the prominence of inverse agonists, multiple signal transduction pathways, agonist-directed signaling and important clinical roles in neuropsychiatric conditions. Like 5-HT\textsubscript{1} receptors, 5-HT\textsubscript{2} receptors have a seven-transmembrane domain motif but couple to phospholipases C and A\textsubscript{2}. The relative efficiency of coupling to these effectors varies depending on the cell type being examined.

### 5-HT\textsubscript{2A} Receptors

5-HT\textsubscript{2A} receptors are densely expressed in the forebrain, especially the cortex, and are expressed in both interneurons and pyramidal neurons. Various ligands display complex pharmacological patterns of activity at 5-HT\textsubscript{2A} receptors, ranging from full to partial agonism, and from neutral antagonism to inverse agonistic behavior. These different activities are thought to reflect ligand stabilization of multiple structural conformations which have been resolved by X-ray crystallography in some cases. Structure-activity models have also been tested using site directed mutagenesis. A great deal of biophysical information has been generated using molecular strategies and heterologous expression of 5-HT\textsubscript{2A} receptors. Furthermore, simultaneous analysis of multiple signal transduction mechanisms in cell culture systems has shown that the same ligand may have differing degrees of intrinsic activity for the activation of different second messenger systems by the same population of 5-HT\textsubscript{2A} receptors.\textsuperscript{17}

### Table 1 | Summary of the structure, pharmacology and function of mammalian 5-HT\textsubscript{1} receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>5-HT\textsubscript{1A}</th>
<th>5-HT\textsubscript{1B}</th>
<th>5-HT\textsubscript{1D}</th>
<th>5-HT\textsubscript{1F}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Gene</td>
<td>5q11.2-q13</td>
<td>6q13</td>
<td>1p34.3-36.3</td>
<td>6q14-q15</td>
</tr>
<tr>
<td>Structure</td>
<td>GPCR</td>
<td>GPCR</td>
<td>GPCR</td>
<td>GPCR</td>
</tr>
<tr>
<td>Transduction System</td>
<td>G-protein coupled- K+ current</td>
<td>G-protein coupled-</td>
<td>G-protein coupled-</td>
<td>G-protein coupled-</td>
</tr>
<tr>
<td>Agonists</td>
<td>8-OH-DPAT (R)-UH301</td>
<td>Sumatriptan PNU 109291 L694247</td>
<td>-</td>
<td>LY 344864</td>
</tr>
<tr>
<td>Antagonists</td>
<td>WAY 100 635 (S)-UH301</td>
<td>GR 55562</td>
<td>BRL 15572</td>
<td>-</td>
</tr>
<tr>
<td>Effect on Neurotransmission</td>
<td>↑Acetylcholine</td>
<td>↑5-HT</td>
<td>↑Glutamate</td>
<td>-</td>
</tr>
<tr>
<td>Therapeutic Target</td>
<td>Depression</td>
<td>Agonists</td>
<td>Agonists</td>
<td>Migraine</td>
</tr>
</tbody>
</table>

### Figure 2A | 5-HT\textsubscript{2A} subtype-selective compounds

![TCB-2 (2592)](image1)

5-HT\textsubscript{2A} agonist

![Ketanserin (0908)](image2)

5-HT\textsubscript{2A} antagonist

![MDL 11,939 (0870)](image3)

5-HT\textsubscript{2A} antagonist

![Sarpogrelate (3739)](image4)

5-HT\textsubscript{2A} antagonist
further supports the notion of complex and dynamic structure-activity relationships for 5-HT2A and 5-HT2C receptors.

5-HT has relatively low affinity for the 5-HT2A receptor compared to other 5-HT receptors, with a \( K_i \) in the low micromolar range. It can be argued however that the high affinity, active conformational state has roughly ten-fold higher affinity for 5-HT2A. Several agonists, such as DOI and LSD, have high affinity for 5-HT2A receptors and others demonstrate selective potency for stimulating one signal transduction pathway over another (e.g. TCB-2). These, however are not particularly selective as they also bind to other 5-HT2 receptors. Several well-characterized antagonists display high selectivity for 5-HT2A receptors, including ketanserin and MDL 100907. A number of others have high affinity but their specificity is not fully described. Some 5-HT2A receptor agonists produce psychotomimetic effects (most famously LSD), and therefore several antipsychotic medications are high affinity 5-HT2A receptor antagonists.

### 5-HT2B Receptors

5-HT2B receptors are sparsely expressed in discrete subregions of CNS, but are heavily expressed in liver, kidney, heart and the fundus of the stomach. This pattern of expression differs from 5-HT2A and 5-HT2C receptors, which are expressed at relatively higher levels in the CNS. They share affinity for many of the same drugs, but a few highly selective 5-HT2B receptor antagonists have been described, including RS 127445. The physiological role of 5-HT2B Receptors is still unclear, but they have been implicated in cardiac function, morphogenesis, and anxiety. 5-HT2B receptors have similar signal transduction coupling to other 5-HT2 receptors in vitro, but less evidence has accumulated for endogenous receptors.

### 5-HT2C Receptors

5-HT2C receptors are strongly expressed throughout the CNS but are expressed at lower levels outside the brain. They are unique among the 5-HT receptors because the mRNA transcript can be edited, leading to subtle changes in coding sequence that can have functionally relevant impacts on the mature receptor protein.\(^{18}\) 5-HT2C receptor knockout mice have been generated which interestingly develop mid-life obesity, glucose intolerance and seizures.\(^{19}\) The pharmacology of 5-HT2C receptors is similar to the other 5-HT2 receptors; they display complex interactions with signal transducing mechanisms, agonist directed signaling and inverse agonism by some atypical antipsychotics. Evidence from animal models indicates that 5-HT2C receptors may impact anxiety, appetite, addiction, and antipsychotic drug actions. SB 242084 is a fairly selective 5-HT2C receptor antagonist with anxiolytic activity. There are no highly selective 5-HT2C agonists developed to date as those described also have affinity for other 5-HT, receptors. Lorcaserin displays some selectivity for the 5-HT2C receptor, although there are no readily available sources for this molecule outside of custom synthesis.\(^{20}\)

### The 5-HT3 Receptor

The 5-HT3 receptor is the only 5-HT receptor that is a member of the Cys-loop ligand-gated ion channel family.\(^{21}\) The receptor complex is thought to be pentameric which is consistent with other Cys-loop LGIC family members.\(^{22}\) This complex may be formed by a combination of up to 5 different subunits, named 5-HT3A-E, although at present only the 5-HT3A and 5-HT3B subunits have been studied in detail. The 5-HT3 receptor complex is a non-selective cation channel (most permeable to Ca\(^{2+}\), Na\(^+\) and K\(^+\) ions) that mediates fast synaptic depolarization neurotransmission in the brain and is prone to rapid desensitization. Recent attention has focused on the combination of subunits forming the functional channel in native tissue. Expression of the 5-HT3A subunit alone in recombinant systems produces a functional receptor that displays many characteristics of native receptors. The caveat is that homomeric 5-HT3A receptors do not generate a relatively high single channel conductance receptor, something that is evident in some populations of native neuronal receptors. Most significantly, co-expression of the 5-HT3A and 5-HT3B subunits results in a heteromeric receptor that mimics the high single channel conductance of some populations of native receptors more faithfully.\(^{23,24}\) In addition to 5-HT, 5-HT3 receptor action is modulated allosterically by volatile anesthetics and alcohols.\(^{25,26,27}\) The actions
of these compounds may, however, depend on the subunit composition of the receptor.\(^{28}\)

Within the brain, the highest densities of 5-HT\(_3\) receptors are associated with the brainstem nuclei encompassing the chemoreceptor trigger zone; namely the dorsal motor nucleus of the vagus nerve, area postrema and nucleus tractus solitarius.\(^{29}\) The 5-HT\(_3\) receptor is also expressed in human forebrain regions including the hippocampus, amygdala and caudate-putamen.\(^{30}\) Of note, expression within the extrapyramidal system (caudate-putamen [striatum] and substantia nigra) is not readily detectable in other species (such as rodents and/or non-human primates).

The 5-HT binding site within the 5-HT\(_3\) receptor complex is constructed by two adjacent N-termini from neighboring subunits in the pentameric complex. Structural analysis has identified that three peptide loops (designated A, B and C) contribute from the ‘principal’ subunit and a further three peptide loops from the ‘complementary’ subunit (D, E and F) participate in ligand binding. Hence, the initial report concerning the stoichiometry of the heteromeric 5-HT\(_3\)AB receptor (with a subunit composition B-A-B-B-A) generated much debate concerning the potential to identify pharmacological compounds that would discriminate homomeric 5-HT\(_3\)A receptors from heteromeric 5-HT\(_3\)AB receptors. The binding sites of the former would arise from A-A interfaces, whereas this structural interface was absent in heteromeric 5-HT\(_3\)AB receptors. Recently, however, the B-A-B-B-A stoichiometry has been questioned.\(^{31}\)

The majority of compounds investigated so far appear unable to discriminate between molecular isoforms of the 5-HT\(_3\) receptor. A notable exception is picrotoxin, which displays weak (micromolar) affinity but good selectivity (approx. 100-fold for homomeric mouse 5-HT\(_3\)A versus heteromeric mouse 5-HT\(_3\)AB receptors).\(^{32}\) This has been demonstrated in functional recordings and the molecular interaction is likely to be a channel blockade of the 5-HT\(_3\) receptor rather than competition at the 5-HT binding site.

Whilst the search continues for the identification of compounds that discriminate readily between 5-HT\(_3\) receptor molecular isoforms, a large number of ligands exist that display high selectivity for the 5-HT\(_3\) receptor versus other neurotransmitter receptors. Initial examples of selective antagonists with nanomolar affinity arose in the 1980s with compounds such as ondansetron, granisetron and tropisetron (although the latter also has micromolar affinity for the 5-HT\(_4\) receptor). All three of these compounds were subsequently approved as drugs to reduce emesis (nausea and vomiting). Subsequently second generation compounds have been developed such as alosetron and palonosetron. These have very high affinity for the 5-HT\(_3\) receptor and have also gained regulatory approval as medicines; the former for irritable bowel syndrome (IBS), whilst the latter appears to display particularly long-lasting antiemetic actions. Indeed this long duration of action of palonosetron would appear to be considerably more than would be predicted from its metabolic half-life and some evidence suggests that this antagonist induces internalization of 5-HT\(_3\) receptors.\(^{33}\)

Table 2 | Summary of the structure, pharmacology and function of mammalian 5-HT\(_{2-3}\) receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>5-HT(_{2A})</th>
<th>5-HT(_{3B})</th>
<th>5-HT(_{3C})</th>
<th>5-HT(_{3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Gene</td>
<td>13q14–q21</td>
<td>2q36.3–2q37.1</td>
<td>Xq24</td>
<td>11q23.1-23.2 (A)</td>
</tr>
<tr>
<td>Structure</td>
<td>GPCR</td>
<td>GPCR</td>
<td>GPCR</td>
<td>LGIC</td>
</tr>
<tr>
<td>Transduction System</td>
<td>↑PLC</td>
<td>↑PLC</td>
<td>↑PLC</td>
<td>Ion conductance (K(^{+}), Na(^{+}), Ca(^{2+}))</td>
</tr>
<tr>
<td>Agonists</td>
<td>DOI</td>
<td>DOI</td>
<td>DOI</td>
<td>2-methyl 5-HT</td>
</tr>
<tr>
<td>Antagonists</td>
<td>Ketanserin</td>
<td>RS 127445</td>
<td>SB 242084</td>
<td>5-HT</td>
</tr>
<tr>
<td>Effect on Neurotransmission</td>
<td>↑Glutamate</td>
<td>↑Dopamine</td>
<td>↑Dopamine</td>
<td>Tropisetron</td>
</tr>
<tr>
<td>Therapeutic Target</td>
<td>Depression</td>
<td>Anxiety</td>
<td>Anxiety</td>
<td>Emesis</td>
</tr>
</tbody>
</table>

Note: The table above provides a summary of the structure, pharmacology, and function of mammalian 5-HT\(_{2-3}\) receptors. Further details can be found in the referenced literature.
In addition to antagonists, there are also high affinity and selective agonists for the 5-HT₃ receptor, although these tend to be partial agonists similar to the non-selective exogenous agonist, 2-methyl-5-HT. Some examples of partial agonists are pumosetrag (DDP733), PBG and mCPBG; SR 57227A is a good example of an exogenous near full agonist.

Activation of the 5-HT₃ receptor modulates release of various neurotransmitters, including a facilitation of dopamine, GABA and 5-HT release, although the receptor is not thought to be expressed by 5-HT neurons.³⁴,³⁵ Conversely, the 5-HT₃ receptor has an inhibitory effect on acetylcholine release in the cortex.³⁶,³⁷ This is likely to be mediated via GABAergic interneurons.³⁸

A number of 5-HT₃ receptor ligands – including odansetron, granisetron, tropisetron and palonosetron – have now been exploited for therapeutic benefit from their ability to alleviate the nausea and vomiting resulting from anticancer chemo- and radiotherapy and also post-operative emesis particularly evident following procedures involving the abdomen.³⁹

A further therapeutic utility of 5-HT₃ receptor ligands concerns the symptomatic relief from IBS. IBS is a recognized heterogeneous condition, which, although not life-threatening, presents a considerable health and economic burden. The potent and selective 5-HT₃ receptor antagonist, alosetron, displays clear efficacy in reducing the symptoms of IBS-d (IBS presenting with diarrhea). Marketing approval for this medication was withdrawn due to rare occurrences of potentially fatal ischemic colitis. This side-effect was also noted – again at a relatively low incidence – in the aborted trials of another 5-HT₃ receptor antagonist, cilansetron, suggesting this side-effect is not an ‘off-target’ phenomenon. The relatively high number of patients that have received 5-HT₃ receptor antagonists to control emesis – without a single report of ischemic colitis - suggests this side effect results from the combination of 5-HT₃ receptor antagonism and the IBS condition.

Significantly, patient pressure assisted the reinstatement of alosetron, albeit with limited availability. In Japan, however, regulatory approval exists for the use of a very low dose of the selective 5-HT₃ receptor antagonist, ramosetron with a maximum daily dose of 10 μg. This very low dose presumably reduces the occurrence of ischemic colitis by limiting the degree of blockade of the 5-HT₃ receptor, although the levels of efficacy achieved by these low doses are open to question. An alternative pharmacological strategy targeting the 5-HT₃ receptor has also been evaluated for IBS-c (IBS presenting with constipation). Here the predicted prokinetic action of a 5-HT₃ receptor partial agonist, DDP733, was assessed; unfortunately the compound displayed relatively high levels of agonist activity (intrinsic activity) such that the compound caused emesis in some patients (predictable for 5-HT₃ receptor agonists with high intrinsic activity). The potential efficacy of 5-HT₃ receptor antagonists to reduce behaviors likely to be mediated via the forebrain (for example anxiety, cognitive dysfunction, and alcohol-induced reward) is not fully understood. Indeed the initial potential of antagonists as therapies for these effects failed to translate in consistent clinical findings. A potential explanation for this is the considerable differences apparent in the cellular and regional expression of the 5-HT₃ receptor when comparing laboratory animals (rodents and New World primates) with humans. Interestingly, some effects of 5-HT₃ receptor antagonists have been identified in humans without prior identification in animal models including fibromyalgia and chronic fatigue syndrome.

**The 5-HT₄ Receptor**

Consistent with other GPCRs, a functional 5-HT₄ receptor protein arises from a single gene. Arising mRNA, however, can be alternatively spliced within the region corresponding to the extracellular link between the fourth and fifth transmembrane domain and the region corresponding to the C-terminus. This produces ten isoforms – 5-HT₄α₁-9, 5-HT₄β₁-2, 5-HT₄δ and 5-HT₄ε – although it is possible that even more will become apparent. With the exception of the 5-HT₄δ receptor isoform, 5-HT₄ receptor transcripts are expressed in the brain. With the role of the C-terminus to facilitate subcellular
localization and to communicate receptor activation rather than impact pharmacology of the orthosteric site, it is not surprising that 5-HT$_4$ receptor isoforms do not tend to differ pharmacologically, although functional differences are apparent.

Expression of the 5-HT$_4$ receptor is evident in the brain, gut and cardiovascular tissues. Within the brain, protein and mRNA tend to colocalize indicating a post-synaptic location. Maximal levels of expression are in the basal ganglia, including the substantia nigra, globus pallidus, caudate nucleus, putamen, nucleus accumbens, hippocampus (CA1 and subiculum) and cortex. The 5-HT$_4$ receptor is positively coupled to adenyl cyclase via $G_\alpha$, with receptor activation resulting in neuronal excitability, although coupling to ion channels is also evident. Excitatory 5-HT$_4$ receptors enhance the release of a number of neurotransmitters including cortical acetylcholine, nigral-striatal dopamine and hippocampal 5-HT.

The 5-HT$_4$ receptor is believed to have a role in learning and memory. Many studies have shown that 5-HT$_4$ receptor activation improves performance in various behavioral paradigms of cognitive function. The beneficial effects of 5-HT$_4$ receptor activation may be mediated by facilitation of acetylcholine release in the cerebral cortex. An alternative relevant process is also evident. Excitatory 5-HT$_4$ receptors elicit second messenger responses in native tissue, with receptor activation resulting in neuronal excitability, although coupling to ion channels is also evident. Excitatory 5-HT$_4$ receptors enhance the release of a number of neurotransmitters including cortical acetylcholine, nigral-striatal dopamine and hippocampal 5-HT.

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is likely that it would lack functionality. The rodent 5-ht\textsubscript{5a} receptor, however, would appear capable of functional expression although little evidence has been generated. 5-ht\textsubscript{5a} receptor mRNA in the rat brain is evident in the hippocampus, habenula, entorhinal and piriform cortices, and the olfactory bulb.

Within heterologous expression systems, the 5-ht\textsubscript{5a} receptor may inhibit adenyl cyclase activity, presumably via G\textsubscript{i}, although other reports have detected no such response. Alternative transduction processes impacted by this receptor may include an increase in intracellular Ca\textsuperscript{2+} mobilization or coupling to an inwardly rectifying potassium channel.

The lack of suitable selective ligands has hampered autoradiographic study of the 5-ht\textsubscript{5a} receptor. 5-ht\textsubscript{5a} receptor protein expression in the rat brain is associated with neurons, and is evident in the hypothalamus, raphe nuclei, locus coeruleus, horizontal nucleus of the diagonal band and amygdala, with more moderate immunoreactivity in the cerebral cortex (particularly entorhinal cortex), hippocampus, lateral habenula, substantia nigra, ventral tegmental area, pons and cerebellum. In situ hybridization using human brain tissue has demonstrated 5-ht\textsubscript{5a} receptor transcripts in the cortex, hippocampus, amygdala and cerebellum.

Although no definitive role for native 5-ht\textsubscript{5a} receptors has been identified, a few studies have suggested putative functions. For instance, 5-ht\textsubscript{5a} receptor knockout mice display enhanced exploratory behavior in response to a novel environment.

The 5-ht\textsubscript{5a} receptor has also been implicated in the regulation of rodent circadian rhythm, although limited pharmacological tools to probe this receptor complicates interpretation. The most promising compound, SB 699551-A, displays a 30-fold selectivity for the human 5-ht\textsubscript{5a} receptor over other 5-HT receptor subtypes and other neuronal targets, aside from the serotonin transporter, which it impacts at only 10-fold higher concentrations. Unfortunately, SB 699551-A displays inter-species variation in affinity for the 5-ht\textsubscript{5a} receptor and displays relatively low affinity for rodent 5-ht\textsubscript{5a} receptors (pK\textsubscript{i} = 6.3), which further limits the utility of this compound to investigate 5-ht\textsubscript{5a} receptor function through the common rodent paradigms.

5-HT\textsubscript{6} Receptors

The 5-HT\textsubscript{6} receptor is coupled to G\textsubscript{s} to activate adenylyl cyclase and shows moderate affinity for serotonin. It is strongly and selectively expressed in CNS but has species-specific patterns of expression with rat and human showing intense expression in striatum and hippocampus but about 1/10 of the expression level in mice and litter regional variation in different areas of the mouse brain. A 5-HT\textsubscript{6} receptor knockout mouse has been developed but the phenotypic relevance is unclear given the low levels of 5-HT\textsubscript{6} receptor expression in wild-type mice as compared to rat or human. The rat and human 5-HT\textsubscript{6} receptor are more similar pharmacologically to each other than to the mouse receptor. The 5-HT\textsubscript{6} receptor has been found in animal models to offer promise as a target for cognitive enhancement and

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Table 3 | Summary of the structure, pharmacology and function of mammalian 5-HT\textsubscript{4-7} receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>5-HT\textsubscript{4}</th>
<th>5-ht\textsubscript{5a}</th>
<th>5-ht\textsubscript{5b}</th>
<th>5-HT\textsubscript{6}</th>
<th>5-HT\textsubscript{7}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Gene</td>
<td>5q31–q33</td>
<td>7q36</td>
<td>2q11–13 (Non-functional)</td>
<td>1p35–36</td>
<td>10q21–q24</td>
</tr>
<tr>
<td>Structure</td>
<td>GPCR</td>
<td>GPCR</td>
<td>GPCR</td>
<td>GPCR</td>
<td>GPCR</td>
</tr>
<tr>
<td>Transduction System</td>
<td>↑cAMP</td>
<td>?↑cAMP</td>
<td>?Ca\textsuperscript{2+} mobilization</td>
<td>Not Known</td>
<td>↑cAMP</td>
</tr>
<tr>
<td>Agonists</td>
<td>BIMU 8</td>
<td>RS 67506</td>
<td>5-CT</td>
<td>5-CT</td>
<td>-</td>
</tr>
<tr>
<td>Antagonists</td>
<td>GR 113808</td>
<td>SB 204070</td>
<td>SB 699551-A</td>
<td>-</td>
<td>Ro 630563</td>
</tr>
<tr>
<td>Effect on Neurotransmission</td>
<td>↑Acetylcholine</td>
<td>↑Dopamine</td>
<td>15-HT</td>
<td>Not Known</td>
<td>↑Acetylcholine</td>
</tr>
<tr>
<td>Therapeutic Target</td>
<td>Cognition</td>
<td>Anxiety</td>
<td>Not Known</td>
<td>Not Known</td>
<td>Cognitive</td>
</tr>
</tbody>
</table>

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possibly weight loss.\(^{57}\) EMDT, EMD 386088, and WAY 181,187 are relatively selective 5-HT\(_6\) receptor agonists, and a number of selective antagonists have also been developed including SB 399885, SB 258585 and Ro 4368554. The less selective ligands tend to also have high affinity for 5-HT\(_{2A}\) and D\(_2\) receptors. A number of clinically important antipsychotic and antidepressant drugs also share high affinity for this receptor along with their other targets.

**The 5-HT\(_7\) Receptor**

5-HT\(_7\) receptors also couple to G\(_s\) (activating adenylyl cyclase) and are widely distributed in the brain.\(^{58}\) Several splice variants with different patterns of distribution within the CNS have been identified,\(^{59}\) although they do not show meaningful pharmacological distinctions in human isoforms.\(^{60}\) Several atypical antipsychotic and antidepressant drugs have sufficient affinity for this receptor and will occupy it at commonly used dosages. Some ligands traditionally associated with other 5-HT receptors also bind to 5-HT\(_7\) receptors, especially those associated with 5-HT\(_{1A}\), 5-HT\(_{2A}\), and 5-HT\(_{6}\) receptors. A particular compound to note is the agonist, 8-OH-DPAT, a full agonist that has only about ten-fold higher affinity for 5-HT\(_{1A}\) than 5-HT\(_7\) receptors. 5-HT\(_7\) receptors have been implicated in a variety of behavioral and physiological processes, including affective behavior, circadian rhythmicity and vasodilation. 5-HT\(_7\) receptor knockout mice have reduced immobility in the forced swim test consistent with the pharmacological data suggesting that blockade of this receptor can produce antidepressant effects. Several moderately selective agonists have been reported, including AS 19 and LP 12; SB 258719 and SB 269970 are very selective antagonists at 5-HT\(_7\) receptors.

**The 5-HT transporter (SERT)**

The 5-HT transporter (SERT or 5-HTT) is a Na\(^+\)/Cl\(^-\) dependent biogenic amine transporter whose family includes the dopamine (DAT) and noradrenaline (NET) transporters.\(^{61}\) SERT is critical to the functioning of the 5-HT system, limiting 5-HT neurotransmission by removing synaptic neurotransmitter through transport across the presynaptic membrane.\(^{62}\) Following the original sequencing of rat SERT,\(^{63}\) subsequent studies have indicated that the functional complex may exist as an oligomer.\(^{54,65}\)

Within the brain SERT is located throughout 5-HT neurons, and hence displays a distribution at the protein level that closelymatches the regions receiving 5-HT neuron innervation. Indeed, the protein offers a phenotypic marker for 5-HT neurons.\(^{66}\) Consistently, *in situ* hybridization studies demonstrate that SERT transcript expression is associated with the cell bodies of 5-HT neurons.\(^{67}\) In the developing mouse brain however, expression of the transporter occurs transiently in glutamatergic thalamocortical afferents that lack the ability to synthesize 5-HT.\(^{68,69}\) These neurons may therefore sequester 5-HT, enabling the afferents to mediate serotonergic transmission during brain development.

More than one form of SERT protein appears to be present *in vivo*. Shigematsu and colleagues conducted immunohistochemical studies on the mouse brain with two selective antibodies, raised against different epitopes within the C- and N-terminus.\(^{70}\) They observed that immunoreactivity with the N-terminal antibody was absent in the CA3 field of the hippocampus, whereas the C-terminal antibody indicated SERT expression. This implies that SERT may contain variable N-terminal domains, potentially though alternative splicing of exon 1. Further molecular diversity appears to be apparent in human immune cells, where SERT may function to deliver 5-HT to other immune cells across the immunological synapse.\(^{71}\)

The efficacy of a range of antidepressant drugs, in particular the selective serotonin reuptake inhibitors (SSRIs), has encouraged elucidation of the physiological roles of SERT in the brain. It is indisputable that the transporter has an effect upon depression, though its precise function is still debated. Further evidence comes from the genetic variation that occurs upstream of the SERT coding sequence, the so-called 5-HTT gene-linked polymorphic region (5-HTTLPR). A series of repeated units incorporated within this sequence forms a promoter region regulating SERT expression.\(^{72,73}\) One common polymorphism within this region is a 44 base pair deletion, denoted as a short form (S) for the gene, along with two variations of a long form (LG and
The short form allele reduces SERT expression and function relative to the long forms.\textsuperscript{72,74} It has been reported however, that LG may result in SERT expression comparable with the short form variant\textsuperscript{75} and the short allele may not be associated with reduced SERT levels in the adult brain,\textsuperscript{76} complicating the research area. Individuals carrying at least one short form allele appear predisposed to depressive episodes. In further support from \textit{in vivo} imaging, SERT expression is reduced within the brainstem,\textsuperscript{77} amygdala and midbrain\textsuperscript{78} in patients presenting with depression.

A number of reports correlate SERT expression with the brains of suicide victims although this area remains controversial.\textsuperscript{79} SERT knockout mice do however display behavioral abnormalities related to depression and anxiety.\textsuperscript{80,81}

In contrast to SERT being a molecular therapeutic target, it is also a target for various drugs of abuse, including MDMA (‘ecstasy’) and cocaine. MDMA, for example, blocks 5-HT reuptake and enhances 5-HT release.\textsuperscript{82,83} Whilst cocaine is predominantly considered to act upon DAT, SERT interaction appears to contribute to the rewarding actions of cocaine.\textsuperscript{84}

**Conclusion**

From the initial discovery of serotonin in the mid-twentieth century, the 5-HT receptor research field continues to expand both scientifically and commercially. Over the last sixty years, considerable physiological and pharmacological processes involving 5-HT receptors and the 5-HT transporter have been identified. The consecutive discovery of the 6 classes of G-protein coupled 5-HT receptors (5-HT\textsubscript{1,2,4-7}) and their subclasses along with the ligand-gated ion channel 5-HT\textsubscript{3} has provided an exciting research platform that holds promise for future drug discovery. Both 5-HT\textsubscript{6} and 5-HT\textsubscript{1A} receptors are relatively uncharacterized and the generation of selective ligands for these receptors may well aid our understanding of their functions \textit{in vivo}. One of the most significant problems in this field has been the absence of sufficiently selective ligands to identify the relative contribution of multiple serotonin receptors to complex behavioral and physiological phenomena mediated by serotonin. As new molecular and pharmacological tools become available, targeting specific 5-HT receptors should lead to the development of many compounds of therapeutic value that will reduce the potential for undesired side effects. The future holds the promise for a new generation of serotonergic drugs that may be useful as antidepressant, antipsychotic, procognitive, and antiemetic treatments. It can be anticipated that 5-HT receptor research will continue to progress and yield exciting results in the years to come.
References

Neuronal 5-HT Receptors

5-HT\textsubscript{1} Receptors

5-HT\textsubscript{1A} Agonists

<table>
<thead>
<tr>
<th>Compound</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0556 BP-554 maleate</td>
<td>Selective 5-HT\textsubscript{1A} agonist</td>
</tr>
<tr>
<td>1006 BMY 7378 dihydrochloride</td>
<td>5-HT\textsubscript{1A} partial agonist</td>
</tr>
<tr>
<td>0962 Buspirone hydrochloride</td>
<td>5-HT\textsubscript{1A} partial agonist</td>
</tr>
<tr>
<td>0529 8-Hydroxy-DPAT hydrobromide</td>
<td>Selective 5-HT\textsubscript{1A} agonist. Also has moderate affinity for 5-HT\textsubscript{1B}</td>
</tr>
<tr>
<td>1080 (R)-(+) 8-Hydroxy-DPAT hydrobromide</td>
<td>Selective 5-HT\textsubscript{1A} agonist. More active enantiomer of 8-Hydroxy-DPAT hydrobromide (Cat. No. 0529)</td>
</tr>
<tr>
<td>0797 8-Hydroxy-PIPAT oxalate</td>
<td>High affinity 5-HT\textsubscript{1A} agonist</td>
</tr>
<tr>
<td>2399 Indorepine hydrochloride</td>
<td>5-HT\textsubscript{1B}, 5-HT\textsubscript{1A} and 5-HT\textsubscript{1C} agonist</td>
</tr>
<tr>
<td>1869 Ispapirone</td>
<td>Selective 5-HT\textsubscript{1A} agonist</td>
</tr>
<tr>
<td>0411 MDL 73005F hydrochloride</td>
<td>Potent and selective 5-HT\textsubscript{1A} partial agonist</td>
</tr>
<tr>
<td>1746 Nemonapride</td>
<td>Highly potent D\textsubscript{2} like antagonist. Also 5-HT\textsubscript{1A} agonist</td>
</tr>
<tr>
<td>0912 RU 24969 hemisuccinate</td>
<td>5-HT\textsubscript{1A} agonist</td>
</tr>
<tr>
<td>1771 S 14506 hydrochloride</td>
<td>Highly potent 5-HT\textsubscript{1A} agonist; displays unique binding mechanism</td>
</tr>
<tr>
<td>2854 Tandospirone hydrochloride</td>
<td>Selective 5-HT\textsubscript{1A} partial agonist</td>
</tr>
<tr>
<td>2739 U 92016A</td>
<td>Selective 5-HT\textsubscript{1A} agonist</td>
</tr>
<tr>
<td>1772 Urapidil hydrochloride</td>
<td>(\alpha) antagonist. Also 5-HT\textsubscript{1A} receptor agonist</td>
</tr>
<tr>
<td>2491 Xaliproden hydrochloride</td>
<td>Orally active, high affinity 5-HT\textsubscript{1A} agonist</td>
</tr>
</tbody>
</table>

5-HT\textsubscript{1B} Agonists

<table>
<thead>
<tr>
<th>Compound</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0553 N-\textsubscript{N}AN-190 hydrobromide</td>
<td>5-HT\textsubscript{1B} agonist</td>
</tr>
<tr>
<td>0994 Pindolol</td>
<td>5-HT\textsubscript{1A/B} antagonist. Also (\beta)-adrenergic antagonist</td>
</tr>
<tr>
<td>1060 (S)-(+) Pindolol</td>
<td>5-HT\textsubscript{1A/B} antagonist. Also (\beta)-adrenergic antagonist. More active enantiomer of pindolol (Cat. No. 0994)</td>
</tr>
<tr>
<td>1516 SDZ 21009</td>
<td>(\beta)-adrenoceptor antagonist. Also 5-HT\textsubscript{1A/B} antagonist</td>
</tr>
<tr>
<td>0631 Spirotramine</td>
<td>5-HT\textsubscript{1A} agonist</td>
</tr>
<tr>
<td>1253 (S)-WAY 101135 dihydrochloride</td>
<td>Potent, selective 5-HT\textsubscript{1A} antagonist</td>
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</table>

5-HT\textsubscript{1D} Agonists

<table>
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<tr>
<th>Compound</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0703 Anipirtolone hydrochloride</td>
<td>Highly potent 5-HT\textsubscript{1D} agonist. Also 5-HT\textsubscript{1A} antagonist</td>
</tr>
<tr>
<td>0638 CGS 12066B dimaleate</td>
<td>5-HT\textsubscript{1D} agonist</td>
</tr>
<tr>
<td>1032 CP 93129 dihydrochloride</td>
<td>5-HT\textsubscript{1D} agonist</td>
</tr>
<tr>
<td>1317 CP 94253 hydrochloride</td>
<td>Potent, selective 5-HT\textsubscript{1A} agonist</td>
</tr>
<tr>
<td>3665 Dontriptan hydrochloride</td>
<td>5-HT\textsubscript{1D} agonist</td>
</tr>
<tr>
<td>3862 Eteriptan hydrochloride</td>
<td>Orally active, selective 5-HT\textsubscript{1D} agonist</td>
</tr>
<tr>
<td>1860 Eltoprazine hydrochloride</td>
<td>5-HT\textsubscript{1} receptor agonist/partial agonist</td>
</tr>
<tr>
<td>2399 Indorepid hydrochloride</td>
<td>5-HT\textsubscript{1B}, 5-HT\textsubscript{1D} and 5-HT\textsubscript{1A} agonist</td>
</tr>
<tr>
<td>0901 5-Noroxytropine oxalate</td>
<td>Selective 5-HT\textsubscript{1A} agonist</td>
</tr>
<tr>
<td>0912 RU 24969 hemisuccinate</td>
<td>5-HT\textsubscript{1A/B} agonist</td>
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5-HT\textsubscript{2} Receptors

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<thead>
<tr>
<th>Compound</th>
<th>Description</th>
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<tbody>
<tr>
<td>0993 Cyanopindolol hemifumurate</td>
<td>5-HT\textsubscript{2A}, 5-HT\textsubscript{2B} antagonist. Also (\beta)-adrenergic antagonist</td>
</tr>
<tr>
<td>1054 GR 55562 dihydrochloride</td>
<td>5-HT\textsubscript{2A} antagonist</td>
</tr>
<tr>
<td>1477 GR 127935 hydrochloride</td>
<td>Potent, selective 5-HT\textsubscript{1A/B} antagonist</td>
</tr>
<tr>
<td>0992 Isamoihene hemifumurate</td>
<td>5-HT\textsubscript{2A} antagonist</td>
</tr>
<tr>
<td>3350 LY 339558</td>
<td>Dual 5-HT\textsubscript{1A/B} antagonist and 5-HT re-uptake inhibitor</td>
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<tr>
<td>5-HT&lt;sub&gt;1D&lt;/sub&gt;</td>
<td><strong>Agonists</strong></td>
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<tr>
<td>3783</td>
<td>CP-135807</td>
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<tr>
<td>3665</td>
<td>Donitrtripan hydrochloride</td>
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<tr>
<td>3862</td>
<td>Eliotryptan hydrobromide</td>
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<td>0864</td>
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<td>0781</td>
<td>L-694,247</td>
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<tr>
<td>2640</td>
<td>L-703,664 succinate</td>
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<td>2556</td>
<td>PNU 109231</td>
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<th>5-HT&lt;sub&gt;2A&lt;/sub&gt;</th>
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<tbody>
<tr>
<td>2643</td>
<td>DOI hydrochloride</td>
<td>Mixed 5-HT&lt;sub&gt;2A&lt;/sub&gt; agonist</td>
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<td>2201</td>
<td>PNU 22394 hydrochloride</td>
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<tr>
<td>2592</td>
<td>TCB-2</td>
<td>Potent, high affinity 5-HT&lt;sub&gt;2A&lt;/sub&gt; agonist</td>
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<table>
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<tbody>
<tr>
<td>3041</td>
<td>CP 890101 hydrochloride</td>
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<td>0875</td>
<td>m-CPP hydrochloride</td>
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<tr>
<td>2643</td>
<td>DOI hydrochloride</td>
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</tr>
<tr>
<td>1860</td>
<td>Eltoprazine hydrochloride</td>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt; receptor agonist/partial agonist</td>
</tr>
<tr>
<td>2399</td>
<td>Indoreterine hydrochloride</td>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt;&lt;sub&gt;/5-HT&lt;sub&gt;1D&lt;/sub&gt;&lt;/sub&gt; agonist</td>
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<tr>
<td>3017</td>
<td>1-Methylpsilocine</td>
<td>Potent and selective 5-HT&lt;sub&gt;2C&lt;/sub&gt; agonist</td>
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<table>
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<td>0875</td>
<td>m-CPP hydrochloride</td>
<td>5-HT&lt;sub&gt;2B&lt;/sub&gt; receptor agonist</td>
</tr>
<tr>
<td>0557</td>
<td>α-Methyl-5-hydroxytryptamine maleate</td>
<td>5-HT&lt;sub&gt;2B&lt;/sub&gt; agonist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5-HT&lt;sub&gt;1A&lt;/sub&gt;</th>
<th><strong>Agonists</strong></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>1885</td>
<td>PNU 142633</td>
<td>Highly selective 5-HT&lt;sub&gt;1A&lt;/sub&gt; agonist</td>
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</tbody>
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<table>
<thead>
<tr>
<th>5-HT&lt;sub&gt;1E&lt;/sub&gt;</th>
<th><strong>Antagonists</strong></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>1207</td>
<td>BRL 15572 hydrochloride</td>
<td>Selective human 5-HT&lt;sub&gt;1E&lt;/sub&gt; antagonist</td>
</tr>
<tr>
<td>1477</td>
<td>GR 127935 hydrochloride</td>
<td>Potent, selective 5-HT&lt;sub&gt;1E&lt;/sub&gt; agonist</td>
</tr>
<tr>
<td>3078</td>
<td>LY 310762 hydrochloride</td>
<td>5-HT&lt;sub&gt;1E&lt;/sub&gt;-preferring antagonist</td>
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<tr>
<td>3350</td>
<td>LY 393558</td>
<td>Dual 5-HT&lt;sub&gt;1B&lt;/sub&gt;/6 and 5-HT&lt;sub&gt;1E&lt;/sub&gt; reuptake inhibitor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5-HT&lt;sub&gt;1F&lt;/sub&gt;</th>
<th><strong>Antagonists</strong></th>
<th></th>
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<tbody>
<tr>
<td>1129</td>
<td>BRL-54443</td>
<td>Potent 5-HT&lt;sub&gt;1F&lt;/sub&gt;/5-HT&lt;sub&gt;6&lt;/sub&gt; agonist</td>
</tr>
<tr>
<td>1129</td>
<td>BRL-54443</td>
<td>Potent 5-HT&lt;sub&gt;1F&lt;/sub&gt;/5-HT&lt;sub&gt;6&lt;/sub&gt; agonist</td>
</tr>
<tr>
<td>3079</td>
<td>LY 334370 hydrochloride</td>
<td>Selective 5-HT&lt;sub&gt;1F&lt;/sub&gt; agonist</td>
</tr>
<tr>
<td>2451</td>
<td>LY 344864 hydrochloride</td>
<td>Potent, selective 5-HT&lt;sub&gt;1F&lt;/sub&gt; agonist</td>
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</table>

<table>
<thead>
<tr>
<th>5-HT&lt;sub&gt;2A&lt;/sub&gt;</th>
<th><strong>Antagonists</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3346</td>
<td>ATC 0175 hydrochloride</td>
<td>MCH1 antagonist; also 5-HT&lt;sub&gt;2A&lt;/sub&gt; antagonist and partial agonist of 5-HT&lt;sub&gt;1A&lt;/sub&gt;</td>
</tr>
<tr>
<td>3077</td>
<td>LY 272015 hydrochloride</td>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt; antagonist, orally active</td>
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<tr>
<td>2993</td>
<td>RS 127445 hydrochloride</td>
<td>Selective, high affinity 5-HT&lt;sub&gt;2A&lt;/sub&gt; antagonist</td>
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<tr>
<td>1371</td>
<td>SB 20066 hydrochloride</td>
<td>Potent 5-HT&lt;sub&gt;2A&lt;/sub&gt; antagonist</td>
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<tr>
<td>1372</td>
<td>SB 204741</td>
<td>Potent, selective 5-HT&lt;sub&gt;2A&lt;/sub&gt; antagonist</td>
</tr>
<tr>
<td>1661</td>
<td>SB 206553 hydrochloride</td>
<td>Potent, selective 5-HT&lt;sub&gt;2A&lt;/sub&gt;/5-HT&lt;sub&gt;1B&lt;/sub&gt; antagonist. Orally active</td>
</tr>
<tr>
<td>1379</td>
<td>SB 221284</td>
<td>Potent, selective 5-HT&lt;sub&gt;2A&lt;/sub&gt; antagonist</td>
</tr>
<tr>
<td>1375</td>
<td>SB 228357</td>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt; antagonist/inverse agonist</td>
</tr>
<tr>
<td>1255</td>
<td>SDZ SER 082 fumarate</td>
<td>Selective 5-HT&lt;sub&gt;2A&lt;/sub&gt;/5-HT&lt;sub&gt;6&lt;/sub&gt; antagonist</td>
</tr>
</tbody>
</table>
Agonists
0440 m-Chlorophenylbiguanide hydrochloride
Potent and specific 5-HT, agonist
0558 2-Methyl-5-hydroxytryptamine hydrochloride
5-HT, agonist/potent 5-HT, ligand
0566 N-Methylquinazaine dimaleate
5-HT, agonist
0969 1-Phenylnylbiguanide hydrochloride
5-HT, agonist
0829 Quipazine dimaleate
5-HT, agonist
0988 RS 56812 hydrochloride
5-HT, partial agonist
1205 SR 57227A hydrochloride
Potent, selective 5-HT, agonist
0666 3-AQUAL
5-HT, antagonist
2759 B-HT 920
D_2 receptor agonist. Also α_1, agonist and 5-HT, antagonist
2903 Granisetron hydrochloride
5-HT, antagonist
0640 MDL 72222
5-HT, antagonist
2018 Mirtazepine
Potent 5-HT, antagonist. Also 5-HT, H, and α_2-agonist. Antidepressant
2844 Mosapride citrate
5-HT, agonist and 5-HT, antagonist
2891 Ondansetron hydrochloride
Selective 5-HT, antagonist
2037 SDZ 205-557 hydrochloride
5-HT,5-HT receptor antagonist
0641 Tropanyl 3,5-dimethylbenzoate
5-HT, antagonist
2459 Tropisetron hydrochloride
Potent 5-HT, receptor antagonist; orally active
0380 Y-25130 hydrochloride
Potent, selective 5-HT, antagonist
1795 Zacopride hydrochloride
Highly potent 5-HT, receptor antagonist. Also 5-HT, agonist

5-HT

Agonists
1695 Cisapride
5-HT, agonist; stimulates intestinal ACh release
3089 CJ 033466
Selective 5-HT, partial agonist
3499 ML 10302 hydrochloride
Potent and selective 5-HT, partial agonist
2844 Mosapride citrate
5-HT, agonist and 5-HT, antagonist
0736 2-[1-(4-Piperonyl)piperazinyl]benzothiazole
5-HT, agonist. Also 5-HT, antagonist
0989 RS 67333 hydrochloride
5-HT, partial agonist
0990 RS 67306 hydrochloride
5-HT, partial agonist

Antagonists
0444 Clozapine
5-HT, antagonist. Also dopamine agonist with some D_2 selectivity
1007 N-Desmethyloclozapine
5-HT, antagonist
1644 Mesulergine hydrochloride
5-HT, and 5-HT, antagonist. Also dopamine receptor partial agonist
1050 RS 102221 hydrochloride
Selective 5-HT, antagonist
1371 SB 206046 hydrochloride
5-HT, antagonist
1661 SB 206553 hydrochloride
Potent, selective 5-HT,5-HT antagonist. Orally active
1379 SB 221284
Potent, selective 5-HT,5-HT antagonist; brain penetrant
1255 SDZ 79 082 fumarate
Selective 5-HT,5-HT antagonist

5-HT

General
0524 AMI-193
Selective 5-HT, antagonist
2746 Amperozide hydrochloride
Atypical antipsychotic; high affinity 5-HT, ligand
0460 Cinanserin hydrochloride
Selective 5-HT, antagonist
2863 DOB hydrochloride
Selective 5-HT, agonist
0590 Metergoline
5-HT, antagonist. Also 5-HT, antagonist and 5-HT, ligand. Has moderate affinity for 5-HT, and high affinity for 5-HT,
0997 Mianserin hydrochloride
5-HT, antagonist. Has moderate affinity for 5-ha,
2018 Mirtazapine
Potent 5-HT, antagonist. Also 5-HT, H, and α_2-agonist. Antidepressant
1955 Ritanserin
Potent 5-HT, antagonist

5-HT

Agonists
0458 5-Carboxamidotryptamine maleate
5-HT, agonist and 5-HT antagonist
0524 AMI-193
Selective 5-HT, antagonist
0590 Metergoline
5-HT, antagonist. Also 5-HT, antagonist and 5-HT, ligand. Has moderate affinity for 5-HT, and high affinity for 5-HT,
0997 Mianserin hydrochloride
5-HT, antagonist. Has moderate affinity for 5-ha,
1795 Zacopride hydrochloride
Highly potent 5-HT, receptor antagonist. Also 5-HT, agonist

Antagonists
1322 GR 113808
Potent, selective 5-HT, antagonist
1658 GR 125487 sulfamate
Potent, selective 5-HT, antagonist. Active in vivo
0728 RS 23597-190 hydrochloride
5-HT, antagonist
0991 RS 39604 hydrochloride
5-HT, antagonist
0785 SB 203186 hydrochloride
5-HT, antagonist
2037 SDZ 205-557 hydrochloride
5-HT,5-HT receptor antagonist

5-HT

Agonists
0458 5-Carboxamidotryptamine maleate
5-HT, agonist and 5-HT antagonist
0524 AMI-193
Selective 5-HT, antagonist
0590 Metergoline
5-HT, antagonist. Also 5-HT, antagonist and 5-HT, ligand. Has moderate affinity for 5-HT, and high affinity for 5-HT,
0997 Mianserin hydrochloride
5-HT, antagonist. Has moderate affinity for 5-ha,
1795 Zacopride hydrochloride
Highly potent 5-HT, receptor antagonist. Also 5-HT, agonist

Antagonists
1322 GR 113808
Potent, selective 5-HT, antagonist
1658 GR 125487 sulfamate
Potent, selective 5-HT, antagonist. Active in vivo
0728 RS 23597-190 hydrochloride
5-HT, antagonist
0991 RS 39604 hydrochloride
5-HT, antagonist
0785 SB 203186 hydrochloride
5-HT, antagonist
2037 SDZ 205-557 hydrochloride
5-HT,5-HT receptor antagonist

5-HT

Agonists
2362 EMD 386088 hydrochloride
Potent 5-HT, agonist
0380 Y-25130 hydrochloride
Potent, selective 5-HT, antagonist
1795 Zacopride hydrochloride
Highly potent 5-HT, receptor antagonist. Also 5-HT, agonist

Antagonists
3326 BGC 20-761
High affinity 5-HT, antagonist
3904 WAY 208466
Selective, high affinity 5-HT, agonist
2911 Ro 04-6790
Potent and selective 5-HT, antagonist
3885 Ro 630563
Selective, high affinity 5-HT, antagonist
1961 SB 258558 hydrochloride
Potent, selective 5-HT, antagonist
3368 SB 271046 hydrochloride
Orally active, selective 5-HT, antagonist
3189 SB 399885 hydrochloride
Potent and selective 5-HT, antagonist
3688 SGS 518 oxalate
Selective 5-HT, antagonist

5-HT

Agonists
1968 AS-19
Reported potent 5-HT, agonist
2925 LP 12 hydrochloride
5-HT, agonist
2534 LP 44
High affinity 5-HT, agonist

Antagonists
1523 LY 215840
5-HT,5-HT, antagonist

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